## REMARKS

### Formal Matters

Claims 29-30, 36-40, 46-49, 52-54 are currently pending in this application. Claims 1-28, 31-35, 41-45 and 50-51 were previously canceled.

Applicants note, with appreciation, that several objections and rejections to the claims have been withdrawn.

In view of the Examiner's earlier restriction requirement, applicant retains the right to present withdrawn, cancelled and unclaimed subject matter in continuing prosecution.

### 35 U.S.C. § 112, Second Paragraph

The Office Action maintains the rejection of claims 29, 30, 36-40, 46-49 and 52-54 under 35 U.S.C. § 112, Second Paragraph for being allegedly indefinite for reciting the term "specifically" with reference to an antibody that "specifically binds to a *patched-2* polypeptide."

While Applicants agree that antibodies raised against an antigen may bind an epitope on the antigen to which it was raised, and that same epitope may reside on another similar or unrelated protein, such reactivity is known in the art as a ***cross-reaction*** and not specific binding. Applicants invite the Examiner's attention to a classic textbook on Antibodies, Ivan Roitt, *et al.* IMMUNOLOGY, Grower Medical Publishing Ltd., 1985, p. 6.3 ("Roitt") (a copy is attached for the Examiner's convenience). In Roitt, the two terms are clearly defined and establish the well-known and accepted definitions in the art:

> Antigen-antibody reactions can show a high level of specificity, that is the binding sites of antibodies directed against determinants on one antigen are not complementary to determinants of another antigen…However, when some of the determinants of an antigen, A, are shared by another antigen, B, then a proportion of the antibodies directed to A will also react with B. This is termed *cross reactivity*. The specificity and cross-reactivity expressed by an antiserum are properties which result from the antibody molecules within the serum.
>
> Roitt at 6.3

The Examiner relies on Van Regenmortel to support his rejection. First, it should be noted that Van Regenmortel was published ***after*** the Applicants' priority date and is an inappropriate reference to define a term of art at the time of filing. Moreover, Van Regenmortel itself states:

> The purpose of this paper is not to review our understanding of the process of immune recognition, but rather to discuss the notion of specificity itself and the way this concept has been used in the field of immunology.
>
> Van Regenmortel at pp. 37-38.

Thus, it is clear that Van Regenmortel's discussion of specificity represents a departure or new concept in use of the term "specificity" than the accepted term in general use in the field of immunology at the time of filing. The Examiner relies on this post-filing, commentary (referred to in the Title as "Reflections") without any evidence that it is the prevailing definition of specificity, nor has the Examiner shown that this represents the now-accepted interpretation in the art.

Finally, even an inspection of Van Regenmortel (Figure 1, for example) shows that reactivity of an antibody raised against Antigen 1 with the same epitope as Antigen 2 is referred to as "cross-reactivity," consistent with the discussion in Roitt above.

Applicants believe the reliance on Van Regenmortel is wholly inappropriate, both with respect to the publication date of Van Regenmortel, and due to its nature as "one man's commentary" rather than art-accepted terms. Instead, Applicants earnestly submit that Roitt represents the accepted terminology in the art.

Applicants respectfully request reconsideration and withdrawal of the rejection of Claims 29, 30, 36-40 and 46-49 and 52-54 under 35 U.S.C. § 112, Second Paragraph.

**35 U.S.C. § 103(a)**

The Office Action maintains the rejection of claims 29, 30, 36-40, 46-49 and 52-54 under 35 U.S.C. § 103(a) as allegedly being obvious over Motoyama *et al.*, (1998) *Nat. Genet.* 18(2): 104-106 in view of U.S. Patent No. 5,932,448 to Tso *et al.* ("Tso").

The Examiner concedes that Motoyama does not teach or suggest antibodies that bind to human patched-2 or even mouse patched-2. Furthermore, the Examiner concedes that Motoyama does not teach a patched-2 protein with the claimed sequence identity to SEQ ID NO:2; the protein disclosed by Motoyama is described by the Examiner as "89.3% similar" to SEQ ID NO: 2 (Office Action dated Oct. 30, 2007, p. 6, lines 11-13). The Office Action argues that it would be obvious to use the method described by Tso to produce antibodies against mouse patched-2, and that such antibodies would fall within the scope of the claimed invention. The Examiner also relies on his erroneous interpretation of the term "specifically bind" to support the rejection under 35 U.S.C. § 103(a).

In view of the discussion above, Applicants request that the Examiner reconsider the rejection under 35 U.S.C. § 103 over Motoyama in view of Tso. As stated in Applicants previous response, Motoyama does not teach a polypeptide with the requisite degree of identity to SEQ ID NO:2, and the references (alone or in combination) fail to teach or even suggest antibodies that specifically bind to a polypeptide having the amino acid sequence of SEQ ID NO:2.

As discussed above, when assessing the scope and content of the prior art, the Examiner has relied on an erroneous and inappropriate reference to interpret the term "specifically bind." Thus, the art applied against the claims (Motoyama) is given a broader reach than what Motoyama actually teaches (*i.e.*, the reference does not teach any polypeptide having an amino acid sequence that is at least 95% identical to SEQ ID NO:2). Thus, when considering the prior art as a whole (Motoyama and Tso) and the claimed invention as a whole, there is a significant difference between the claimed invention and the prior art. One of ordinary skill in the art could not produce the claimed invention armed with the disclosures of Motoyama and Tso, nor predict what properties an antibody against a human patched-2 polypeptide would possess.

Applicants earnestly submit that claims 29, 30, 36-40, 46-49 and 52-54 distinguish over Motoyama in view of Tso, and respectfully request withdrawal of the rejection under 35 U.S.C. § 103(a).

## SUMMARY

Claims 29, 30, 36-40, 46, 49 and 52-54 are pending in the application.

If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is strongly encouraged to call the undersigned at the number indicated below.

This response/amendment is submitted within the three month shortened statutory period, and as such, it is believed that no fees are due. However, in the unlikely event that this document is separated from the transmittal letter or if fees are required, applicants petition the Commissioner to authorize charging our Deposit Account 07-0630 for any fees required or credits due and any extensions of time necessary to maintain the pendency of this application.

Applicants respectfully request allowance of the claims as presented herein.

Respectfully submitted,
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Many molecules however, have more than one antigenic determinant. Microorganisms have a very large number of antigenic determinants exposed on their surfaces, hence all these are multivalent. When a multivalent antigen combines with more than one of an antibody's combining sites, the binding energy between the two is considerably greater than the sum of the binding energies of the individual sites involved since all the antigen-antibody bonds must be broken simultaneously before the antigen and antibody will dissociate.

The strength with which a multivalent antibody binds a multivalent antigen is termed *avidity* to differentiate it from the *affinity* of the bond between a single antigenic determinant and an individual combining site. Thus the avidity of an antibody for its antigen is dependent on the affinities of the individual combining sites for the determinants on the antigen, but is greater than the sum of these affinities if both antigen and antibody are multivalent (Fig. 6.6). In normal physiological situations avidity is likely to be more relevant since naturally occurring antigens are multivalent; however, the precise measurement of hapten-antibody reactions is more likely to give an insight into the immunochemical nature of the antigen-antibody reaction.

## ANTIBODY SPECIFICITY

Antigen-antibody reactions can show a high level of specificity, that is, the binding sites of antibodies directed against determinants on one antigen are not complementary to determinants of another antigen. For example, antibodies to a virus like measles will bind to the measles virus and confer immunity to this disease, but will not combine with, or protect against, an unrelated virus such as polio. The specificity of an antiserum is the result of the summation of actions of the various antibodies in the total population each reacting with a different part of the antigen molecule and even different parts of the same determinant (Fig. 6.7). However, when some of the determinants of an antigen, A, are shared by another antigen, B,

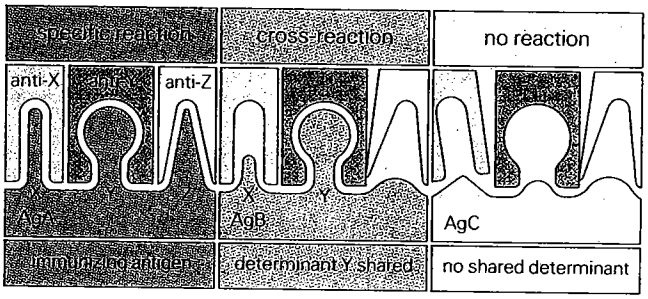


**Fig. 6.7 Specificity, cross-reactivity and non-reactivity.** Antiserum specificity results from the action of a population of individual antibody molecules (anti-X, anti-Y, and anti-Z) directed against different determinants (XYZ) on the antigen molecule (AgA). Antigen A (AgA) and antigen B (AgB) share determinant Y in common. Antiserum raised against AgA (anti-XYZ) not only reacts *specifically* with AgA but *cross-reacts* with AgB (through recognition of shared determinant Y and weak recognition of determinant X'). The antiserum gives *no reaction* with AgC (no shared determinants).

then a proportion of the antibodies directed to A will also react with B. This is termed *cross-reactivity*. The specificity and cross-reactivity expressed by an antiserum are properties which result from the antibody molecules within the serum.

| Radical (R) | sulphonate | arsonate | carboxylate |
|---|---|---|---|
| | tetrahedral | tetrahedral | planar |
| ortho | + + | – | – |
| meta | + + + | + | ± |
| para | ± | – | – |

**Fig. 6.8 An example of specificity and cross-reactivity:** recognition by antibody of overall antigenic structure rather than chemical composition. An antiserum is raised to the meta isomer of amino benzene sulphonate (the immunizing antigen). This antiserum is then reacted with the ortho and para isomers of amino benzene sulphonate and also with the three isomers (ortho, meta, para) of two different but related antigens: aminobenzene arsonate and amino benzene carboxylate. The antiserum reacts specifically with the sulphonate group (which has a tetrahedral structure) in the meta position but will give a cross-reaction (though weaker) with sulphonate in the ortho position. Further, but weaker, cross-reactions are possible when this antiserum is reacted with either the tetrahedral arsonate group or the planar carboxylate group in the meta, but not in the ortho or para position. The arsonate group is larger than sulphonate and has an extra H atom, while the carboxylate is smaller and planar. These results suggest that the overall configuration of the antigen is as important as individual chemical groupings.

There is evidence that the antibody recognizes the overall configuration of the antigen rather than its chemical composition and it is envisaged that antibodies are directed against particular three-dimensional electron cloud shapes rather than specific chemical structures (Fig. 6.8). In addition, there is frequently an inverse relationship between the charge of an antigen and the antibodies it induces (Fig. 6.9).

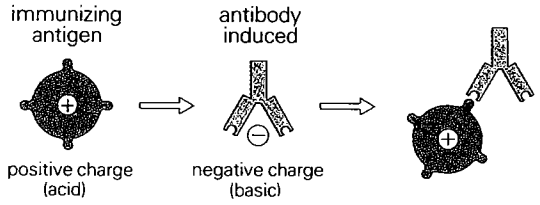


**Fig. 6.9 Charge specificity.** Antigen induces formation of, and complexes with, antibody of a charge opposite to its own.